CHAPTER 9

Stages 0 and I breast cancer

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This chapter focuses on the diagnosis and management of early-stage breast cancer, ie, stages 0 and I disease. This is an important area, since more noninvasive and small breast cancers are being diagnosed due to the increasing use of screening mammography. Treatment of these malignancies will continue to evolve as the results of clinical trials lead to further refinements in therapy.

STAGE 0 BREAST CANCER

Stage 0 breast cancer includes noninvasive breast cancer—lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS)—as well as Paget's disease of the nipple when there is no associated invasive disease.

LOBULAR CARCINOMA IN SITU

LCIS is nonpalpable, produces no consistent mammographic changes, and is often an incidental finding after breast biopsy performed for another reason.

The biologic behavior of LCIS continues to be an issue of debate. Most clinicians agree that it is a marker for increased risk for all types of breast cancer (both noninvasive and invasive).

Epidemiology and etiology

The incidence of LCIS has doubled over the past 25 years and is now 2.8 per 100,000 women. In the past, the peak incidence of LCIS was in women in their 40s. Over the past 3 decades, the peak incidence has increased to the 50s. The incidence of LCIS decreases in women who are in their 60s-80s. It has been suggested that the increase in the age of peak incidence of LCIS is related to the use of hormone replacement therapy (HRT). It is also possible that the use of HRT prevents the usual regression of LCIS normally seen at the time of menopause.

Signs and symptoms

LCIS is nonpalpable and has no consistent features on breast imaging. Most often, LCIS is found in association with a completely separate mammographic abnormality or palpable mass.

Risk of invasive cancer

Approximately 20%-25% of women with LCIS will develop invasive cancer within 15 years after the diagnosis of LCIS. More often, the invasive cancer is ductal in origin, and both breasts are at risk. At this point, there are no reliable molecular markers to determine which patients with LCIS will progress to invasive cancer.

Just as the incidence of LCIS has increased, there has also been an associated increase in the incidence of cases of infiltrating lobular carcinoma in postmenopausal women. The increase in invasive lobular carcinoma peaks in women in their 70s.

Pathology

LCIS appears to arise from the terminal duct-lobular apparatus, and the disease tends to be multifocal, multicentric, and bilateral. Subsequently, other types of LCIS have also been described and include pleomorphic LCIS. This entity tends to be associated with infiltrating lobular carcinoma, and the cytologic features are similar to those of intermediate- or high-grade DCIS. Pleomorphic LCIS may be more aggressive, with a higher likelihood of progression to invasion than classic LCIS.

Treatment options

The management of LCIS is continuing to evolve since the disease appears to be heterogeneous. Presently, treatment options include close follow-up, participation in a chemoprevention trial, tamoxifen, or bilateral prophylactic total mastectomy with or without reconstruction. At present, the decision for a given treatment will depend upon the patient's individual risk profile for DCIS or invasive breast cancer after careful counseling. In the future, treatment decisions may be based upon an analysis of a series of molecular markers, which can separate those patients with a low risk for invasion from those who are at high risk for disease progression.

DUCTAL CARCINOMA IN SITU

DCIS is being encountered more frequently with the expanded use of screening mammography. In some institutions, DCIS accounts for 25%-50% of all breast cancers.

Epidemiology

DCIS, like invasive ductal carcinoma, occurs more frequently in women, although it accounts for approximately 5% of all male breast cancers. The average age at diagnosis of DCIS is 54-56 years, which is approximately a decade later than the age at presentation for LCIS.

Signs and symptoms

The clinical signs and symptoms of DCIS include a mass, breast pain, or bloody nipple discharge. On mammography, the disease most often appears as microcalcifications. Because these microcalcifications are nonpalpable and

are not always associated with a mass, DCIS is often discovered with mammography alone. Approximately 5% of patients who present with pathologic nipple discharge will have underlying breast cancer, and many of them will have DCIS alone.

Risk of invasive cancer

The risk of developing an invasive carcinoma following a biopsy-proven diagnosis of DCIS is between 25% and 50%. Virtually all invasive cancers that follow DCIS are ductal and ipsilateral and generally present in the same quadrant within 10 years of the diagnosis of DCIS. For these reasons, DCIS is considered a more ominous lesion than LCIS (which is considered a marker for risk) and appears to be a more direct precursor of invasive cancer.

Pathology

A variety of histologic patterns are seen with DCIS, including solid, cribriform, and papillary. Some researchers have divided DCIS into two subgroups: comedo and noncomedo types. As compared with the noncomedo subtypes, the comedo variant has a higher proliferative rate, overexpression of HER-2/*neu*, and a higher incidence of local recurrence and microinvasion. DCIS is less likely to be bilateral and has approximately a 30% incidence of multicentricity.

Treatment of noninvasive breast carcinoma

DUCTAL CARCINOMA IN SITU

Breast-conserving surgery

Breast-conservation surgery, followed by radiation therapy to the intact breast, is now considered the standard treatment for patients with DCIS. Since the incidence of positive lymph nodes after axillary lymph node dissection for DCIS is ~1%-2%, axillary dissection is not indicated in most instances.

The most important factor in determining local control within the breast is margin status. A surgical margin of 1 mm has been associated with a 43% chance of having residual disease at the time of reexcision. When a surgical margin of 10 mm can be obtained, there is an extremely low rate of recurrence (4%). A 10-mm surgical margin may not be practical, however, when trying to provide a good cosmetic outcome. When using breast-conserving therapy alone (without irradiation) a margin of at least 10 mm is required, and the tumor should be small (< 1 cm) and a noncomedo type. Although a wide margin is always desirable, narrower margins are acceptable for DCIS when radiation therapy is used after lumpectomy.

Sentinel node biopsy for DCIS

The sentinel lymph node is the first node in the draining lymphatic basin that receives primary lymph flow. The technique of sampling the first draining lymph node was initially described in the management of patients with mela-

noma to determine who would benefit from regional lymph node dissection and was performed using a vital blue dye. This same technique has been used in patients with breast cancer, and sentinel lymph node biopsy represents a minimally invasive way to determine whether the axilla is involved with disease. If the sentinel lymph node is negative, the patient may be spared lymph node dissection. The precise methods for identifying the sentinel lymph node (filtered vs unfiltered Tc-99m sulfur colloid and/or blue dye) and assessing the node (hematoxylin and eosin staining vs immunohistochemistry vs polymerase chain reaction [PCR]) are being studied. The location of the injection is also being evaluated to determine whether there is an advantage to the injection being administered either subdermally or intraparenchymally at the site of the primary tumor or in the periareolar location.

Axillary lymph node dissection is not routinely recommended for patients with DCIS. Recently, however, investigators have used sentinel lymph node biopsy to determine whether individuals with DCIS may harbor occult nodal metastases. Current studies have identified metastatic disease to the axillary nodes in up to 12% of patients who have undergone sentinel lymph node biopsy. Despite this relatively high percentage of positive sentinel nodes, recurrence in the nodal basins is rare (about 2%). Based on this and recent work, there is no indication for routine sentinel lymph node biopsy in patients with DCIS.

Factors associated with an increased risk of axillary metastasis with a diagnosis of DCIS are (1) extensive DCIS requiring mastectomy, (2) suspicion of microinvasion, (3) DCIS associated with a palpable mass, and (4) evidence of lymphovascular permeation or invasion seen on review of the slides. These factors likely are associated with a preoperatively nondiagnosed invasive component. However, for patients diagnosed with DCIS who are scheduled for mastectomy, sentinel lymph node sampling, prior to mastectomy, is a reasonable practice. In the event that an occult invasive cancer within the mastectomy is found, a negative sentinel node would be reassuring and perhaps would make it possible to avoid follow-up axillary dissection.

Technique used in breast cancer In breast cancer, lymphatic mapping has been performed using a vital blue dye and/or lymphoscintigraphy. The primary tumor site is injected with the blue dye or a radioactive tracer, usually technetium-labeled sulfur colloid. When a vital dye is used, the axillary dissection is carefully carried out to identify the blue-stained afferent lymphatic vessels that lead to the sentinel node. When the radioactive tracer is injected peritumorally, a handheld gamma counter is used to locate the sentinel node.

Adjuvant radiation therapy

Retrospective series of patients with DCIS, as well as subsets of patients with early invasive cancer, have been treated with conservative surgery alone, omitting radiation therapy to the intact breast. In addition, several prospective, randomized trials have attempted to address this issue of omission of breast irradiation for both invasive cancer and DCIS. It is clear from all of these series that omission of breast irradiation results in a significantly higher ipsi-

lateral breast tumor recurrence rate but has not, as yet, had an impact on overall survival.

Two large prospective randomized trials have demonstrated a significant reduction in local relapse with the use of postlumpectomy irradiation in treatment of DCIS. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17, local recurrence rates at 8 years were reduced from 27% to 12% with postlumpectomy irradiation.

Similar results were recently reported by a European cooperative group study of 1,010 women with DCIS randomly assigned to receive either 50 Gy of radiotherapy to the whole breast over 5 weeks or no further treatment. With a median follow-up of 4.25 years, the 4-year local relapse-free rate was 91% in the radiotherapy arm vs 84% in the observation arm. Hazard ratios with postexcision radiotherapy were 0.62 for all local relapses, 0.65 for DCIS recurrences, and 0.60 for noninvasive recurrences.

Both trials showed that radiotherapy reduces the risk of both noninvasive and invasive recurrences. Identification of a subgroup of patients who did not benefit from postlumpectomy irradiation has not as yet been clearly defined.

The Van Nuys Prognostic Index (VNPI), based on tumor size, grade, presence of necrosis, and width of the excision margin, is an algorithm commonly used to predict local recurrence after breast-conserving surgery for DCIS. In some series, VNPI lacked discriminatory power for guiding further patient management. In studies performed by this group, it appears that the width of the excision margin is the most important predictor of local recurrence after breast-conserving surgery for DCIS.

One study demonstrated acceptable local control in patients with DCIS treated by excision alone, provided that wide negative margins were obtained. In this retrospective series of 469 patients, radiation therapy did not lower the local recurrence rate in patients with wide (≥ 10 mm) negative margins but did produce a significant benefit in patients with close (≤ 1 mm) margins. The authors concluded that radiation therapy is unlikely to benefit patients with wide negative margins and small tumors. These findings need to be confirmed in prospective, randomized trials.

Although there may be some patients in whom wide excision alone is appropriate therapy, the available literature has not consistently identified a specific subgroup of patients in whom radiation therapy should routinely be omitted. Clearly, the omission of radiation therapy in subsets of patients remains a controversial issue worthy of further investigation. It is hoped that ongoing randomized studies will help resolve some of the controversy generated by selective, retrospective studies.

Adjuvant tamoxifen therapy

Adjuvant therapy is not routinely employed in patients with DCIS. However, the use of tamoxifen for the prevention of secondary breast cancers in women at high risk for breast cancer, which includes women previously diagnosed with DCIS, has led some clinicians to consider the use of tamoxifen in women diagnosed with DCIS. In an NSABP trial (NSABP B-24), 1,804 women

Two recent trials have addressed the need for postlumpectomy radiation therapy (RT) in older women with breast cancer. Both studies randomized patients, following lumpectomy and adjuvant hormonal therapy, to RT or observation. Although both studies confirmed statistically significant improvements in local control with RT, local relapse rates were acceptable in carefully selected patients. The authors concluded that selected elderly patients may be treated with hormonal therapy alone (without RT) following breast-conserving therapy (*Hughes KS, Schnaper LA, Berry D, et al: N Engl J Med 351:971-977, 2004; Fyles AW, McCready DR, Manchul LA, et al: N Engl J Med 351:963-970, 2004*).

with DCIS treated with lumpectomy and irradiation were randomly assigned to receive placebo or tamoxifen. At a median follow-up of 74 months, women in the tamoxifen group had fewer breast cancer events than those in the placebo group (8.2% vs 13.4%; $P = .0009$). Tamoxifen decreased the incidence of both ipsilateral and contralateral events. The risk of ipsilateral invasive cancers was reduced by tamoxifen, regardless of the presence or absence of comedonecrosis or margin involvement.

In a recent analysis of NSABP B-24, it was found that the benefit from tamoxifen is derived exclusively by patients with hormone receptor-positive disease. Based on these results, tamoxifen may be considered as adjuvant therapy in patients with hormone receptor-positive DCIS. The role of tamoxifen or other estrogen receptor modulators is likely to evolve rapidly over the next decade, and additional data on the use of hormonal agents as adjuvant therapy for DCIS are eagerly awaited.

STAGE I BREAST CANCER

Stage I breast cancer ranges from microinvasive tumors (≤ 0.1 cm) to tumors ≤ 2 cm without evidence of spread to the regional lymph nodes.

Pathology of invasive breast cancer

Ductal carcinoma Most cases of invasive carcinomas of the breast are ductal in origin. Of the different histologic subtypes of ductal carcinoma that have been described, tubular, medullary, mucinous (colloid), and papillary subtypes have been associated with a favorable outcome.

Lobular carcinoma Approximately 5%-10% of invasive breast cancers are lobular in origin. This histology has been associated with synchronous and metachronous contralateral primary tumors in as many as 30% of cases.

Treatment of stage I breast cancer

SURGICAL AND RADIATION TREATMENT

Multiple studies have demonstrated that patients with stage I breast cancer who are treated with either breast-conservation therapy (lumpectomy and radiation therapy) or modified radical mastectomy have similar disease-free and overall survival rates.

TABLE 1: Contraindications to breast conservation

Absolute contraindications	Relative contraindications
Multicentric disease[a]	Tumor size vs breast size
Diffuse malignant microcalcifications	Tumor location
Pregnancy	Collagen vascular disease (excluding rheumatoid arthritis)
Persistently positive surgical margins	
Previous breast or mantle irradiation	

[a] If a satisfactory cosmetic outcome is anticipated, multicentric disease is considered to be a relative contraindication.

Breast-conservation therapy

Extent of local surgery The optimal extent of local surgery has yet to be determined and, in the literature, has ranged from excisional biopsy to quadrantectomy. A consensus statement on breast-conserving therapy issued by the National Cancer Institute (NCI) recommended that the breast cancer be completely excised with negative surgical margins.

The extent of axillary surgery also continues to evolve. In recent years, patients with early-stage breast cancer who have clinically node-negative disease have the option to undergo sentinel lymph node biopsy rather than axillary node dissection. Present standard of care for patients with a positive sentinel node is complete nodal dissection. A study is under way to determine whether patients with a positive sentinel node require further axillary surgery.

Patient selection Specific guidelines must be followed when selecting patients for breast conservation. Patients may be considered unacceptable candidates for conservative surgery and radiation therapy either because the risk of breast recurrence following the conservative approach is significant enough to warrant mastectomy or the likelihood of an unacceptable cosmetic result is high. Some patients who are candidates for breast conservation can undergo breast MRI to identify sites of additional disease within the breast that may preclude breast-conserving treatment, although this is not a standard for evaluation. Contraindications to breast-conserving surgery are listed in Table 1.

Risk factors for ipsilateral recurrence For patients undergoing conservative surgery followed by radiation therapy to the intact breast, the risk of ipsilateral breast tumor recurrence has been reported to range from 0.5% to 2.0% per year, with long-term failure rates varying from 7% to 20%. Risk factors for ipsilateral breast tumor recurrence include, but are not limited to, young age (< 35-40 years), an extensive intraductal component, major lymphocytic stromal reaction, peritumoral invasion, presence of tumor necrosis, and positive resection margins. After a wide excision has been performed, the specimen

Initial anecdotal reports have demonstrated higher complication rates in patients with collagen vascular disease (CVD). In a case-controlled study of conservatively managed breast cancer patients, however, researchers at Yale University found no adverse long-term sequelae in patients with CVD, with the exception of patients with scleroderma, who appear to have suboptimal results with radiation therapy (*Chen A, Obedian E, Haffty BG: Cancer J Sci Am 7:480-491, 2001*).

should be oriented and inked; the pathologist may then ink each margin a different color. If a positive surgical margin is present, the color-coded system will guide the reexcision to obtain negative surgical margins with the removal of the least amount of breast tissue possible.

Earlier studies demonstrated that an extensive intraductal component was a risk factor for local relapse. However, in subsequent reports, when negative surgical margins are achieved, patients with an extensive intraductal component can be safely treated with breast conservation. Although it is desirable to achieve negative surgical margins, the available data do not preclude the use of conservative treatment, provided that adequate radiation doses (> 6,000 cGy) to the tumor bed are employed. The role of the remaining risk factors previously cited in predicting recurrence is unclear, and patients should not be denied breast conservation because of their presence.

Cosmetic considerations include primary tumor size and location, overall breast size, total body weight, and a history of preexisting collagen vascular disease.

Tumor size and breast size are important in determining whether the patient will have an acceptable cosmetic outcome after surgical resection. Patients with large tumors with respect to breast size may consider neoadjuvant chemotherapy to reduce the size of the primary tumor and allow breast preservation. (See chapter 11 for discussion of neoadjuvant chemotherapy.)

Obese women with large, pendulous breasts may experience marked fibrosis and retraction of the irradiated breast, making a good to excellent cosmetic outcome less likely. Techniques of brachytherapy may prove beneficial for these women. Women in this situation can undergo bilateral reduction mammoplasty after the wide excision of the primary tumor site has been completed. The partial mastectomy specimen should be evaluated by the pathologist to ensure adequate resection margins. Radio-opaque clips can be left to mark and identify the primary tumor site for the radiation oncologist. The follow-up mammograms will be more difficult to interpret due to scarring and radiotherapy effect.

Patients with collagen vascular disease may develop marked fibrosis and bone necrosis following adjuvant radiation therapy. Most patients with active collagen vascular disease are not candidates for conservative therapy; however, patients with minimal manifestations of the disease or those with rheumatoid arthritis may be considered for breast-preserving treatment.

In some instances, it is necessary to excise skin to obtain a negative surgical margin. This does not necessarily preclude the patient from having breast-conserving therapy and does not mean the patient should have a poor cosmetic outcome. When skin

must be removed to obtain a negative surgical margin, complex skin closures, such as V-Y advancement flaps or Z-plasties, can be utilized to enhance cosmesis.

Patients with centrally located tumors Traditionally, patients who have centrally located tumors requiring excision of the nipple-areolar complex have not been offered the option of breast conservation. However, the cosmetic result achieved after local tumor excision that includes the nipple-areolar complex may not differ significantly from that obtained following mastectomy and reconstruction.

Furthermore, conservatively treated patients with subareolar lesions do not necessarily need to have the nipple-areolar complex sacrificed as long as negative surgical margins can be achieved. However, if the complex is not removed, the remaining breast tissue and overlying skin remain sensate. Recent studies also indicate that the incidence of local recurrence is not increased when primary tumors in this location are treated conservatively.

Genetically predisposed breast cancer patients For women harboring germline mutations in *BRCA1* or *BRCA2*, there are limited data regarding long-term outcome. Studies, to date, have shown acceptable local control rates in the short term and increased but acceptable rates of acute, subacute, and chronic normal tissue reactions with lumpectomy followed by radiation therapy. Women with germline *BRCA1* and *BRCA2* mutations, however, are at high risk for second primary tumors in the contralateral breast.

A study from Yale University demonstrated high rates of second primary tumors in the ipsilateral breast. This study suggests that if breast-conserving therapy is chosen, some prophylactic measures, such as selective estrogen receptor modulators or oophorectomy, might be considered to reduce the risk of second primary tumors in the ipsilateral or contralateral breast. Other studies also indicate a trend toward higher rates of late local relapses in *BRCA* carriers. Further studies are clearly warranted to assess the long-term risks and benefits of breast-conserving strategies in women harboring mutations in *BRCA1* and *BRCA2*.

Role of axillary lymph node dissection The role of axillary lymph node dissection in the management of breast cancer has been questioned, particularly when a patient with a clinically negative axilla is undergoing breast-conservation therapy. In most instances, the breast surgery is performed with the patient under local anesthesia and sedation on an outpatient basis. When axillary lymph node dissection is added, the surgery is performed with the patient under general anesthesia.

It has also been suggested that if the status of the nodes will not change therapy, the dissection is unnecessary and the axilla can be treated with irradiation. On the other hand, if axillary lymph node staging is not performed, the patient will not be accurately staged and important prognostic information will be unavailable.

Patients who may not be candidates for sentinel node biopsy are women who are pregnant or breast-feeding and women who have had prior irradiation. A

prior excisional biopsy does not preclude the use of lymphatic mapping and sentinel node biopsy. It has recently been suggested that sentinel node biopsy accurately evaluates the axilla, even in patients with tumors > 5 cm and those who have been treated with neoadjuvant chemotherapy.

Once the sentinel node(s) have been identified, they can be sent to pathology for frozen section or touch-prep analysis.

Sensitivity and specificity In breast cancer, lymphatic mapping has been performed using a vital blue dye and/or lymphoscintigraphy. Studies have suggested that the success rate for identifying the sentinel node can be increased when these techniques are used in combination. The ability to identify the sentinel node can reach as high as 97% when blue dye and Tc-99m sulfur colloid are used together. When blue dye is used alone, the success rate is 83%, and when Tc-99m sulfur colloid is used alone, the success rate is 94%.

Recent results in a multi-institution practice demonstrate that sentinel lymph node biopsy using dual-agent injection provides optimal sensitivity. In the study, 806 patients were enrolled by 99 surgeons for sentinel lymph node biopsy by single-agent (blue dye alone or radioactive colloid alone) or dual-agent injection at the discretion of the surgeons. All patients underwent complete level I/II dissection following the sentinel procedure. There were no significant differences in the identification of a sentinel node among patients who underwent single- compared with dual-agent injection. However, the false-negative rates were 11.8% for single-agent vs 5.8% for dual-agent injections ($P = .05$).

The sensitivity and specificity of sentinel lymph node biopsy are high, and the likelihood of a false-negative result is extremely low. False-negative rates vary between series, ranging from 0% to 11%. In one series, in 18% of the cases where the frozen-section evaluation of the node was negative, the final pathologic evaluation revealed metastatic disease, and the patient ultimately required lymph node dissection. This potential result can be distressing to patients; however, they should be informed of this possibility at the time of the sentinel lymph node biopsy.

The decision to eliminate axillary lymph node dissection when the sentinel node is negative is being evaluated in a clinical trial. There are, however, many surgeons who are well experienced with the technique and thus have a low false-negative rate. Many of these surgeons are comfortable eliminating a complete axillary dissection in the face of a negative sentinel node biopsy. The decision to eliminate axillary lymph node dissection in the face of a positive sentinel node is being examined by a large clinical trial.

Mastectomy options

Patients who are not candidates for breast conservation or who are not interested in breast conservation are offered mastectomy. For patients who desire immediate reconstruction at the time of mastectomy, a skin-sparing approach is recommended, provided it is oncologically safe. In most instances, the mastectomy can be performed through a circumareolar incision, where the nipple-

areolar complex (NAC) is excised in continuity with the breast tissue. If a biopsy has been performed, this skin should also be excised with the mastectomy specimen. There have been recent reports in the literature in which the NAC has been spared during the course of a skin-sparing mastectomy. This concept awaits further study and is not considered standard of care.

Radiation therapy after breast-conserving surgery

Based on the results of a number of retrospective single-institution experiences, as well as several prospective randomized clinical trials, breast-conserving surgery followed by radiation therapy to the intact breast is now considered a standard treatment for the majority of patients with stage I or II invasive breast cancer.

Radiation dose and protocol Radiation therapy after breast-conservation surgery should employ careful treatment planning techniques that minimize treatment of the underlying heart and lungs. To achieve the optimal cosmetic result, efforts should be made to obtain a homogeneous dose distribution throughout the breast. Doses of 180-200 cGy/d to the intact breast, to a total dose of 4,500-5,000 cGy, are considered standard.

Additional irradiation to the tumor bed is often administered. Although the necessity of a boost to the tumor bed has been questioned, at least two randomized clinical trials have demonstrated a small but statistically significant reduction in ipsilateral breast tumor relapses with the use of a radiation boost to the tumor bed following whole-breast irradiation of 50 Gy. In one of these trials, involving more than 5,000 women randomized to receive either a 16-Gy boost to the tumor bed or not, a 3% absolute reduction in local relapse was seen with the use of the radiation boost (4.3% vs 7.3%, $P < .0001$). This effect was particularly evident in patients younger than age 50. The boost is directed at the original tumor bed with either electron-beam irradiation or an interstitial implant, to bring the total dose to 50-66 Gy.

Regional nodal irradiation For patients who undergo axillary dissection and are found to have negative nodes, regional nodal irradiation is no longer routinely employed. For patients with positive nodes, radiation therapy to the supraclavicular fossa and/or internal mammary chain may be considered on an individualized basis (see chapter 10).

Partial breast irradiation There have been several recent reports demonstrating promising results with the use of partial breast irradiation, a

In a recent meta-analysis evaluating radiation therapy following breast-conserving surgery, a search of the literature identified 15 trials with a pooled total of 9,422 patients available for analysis, who were randomized following breast-conserving therapy to radiation therapy or observation. The relative risk of ipsilateral breast tumor recurrence after surgery was 3.00 (95% CI = 2.65 to 3.40). Mortality data were available for 13 trials, with a pooled total of 8,206 patients. The relative risk of mortality was 1.086 (95% CI = 1.003 to 1.175), corresponding to an estimated 8.6% relative excess mortality if radiotherapy was omitted. The authors concluded that omission of radiotherapy is associated with a large increase in risk of ipsilateral breast tumor recurrence and a small increase in the risk of mortality (*Vinh-Hung V, Verschraegen CL: J Natl Cancer Inst 21:115-121, 2004*).

potentially more convenient option for patients than the extended course of postoperartive radiotherapy.

Additional options are now available that shorten the radiotherapy treatment time to 1-5 days (accelerated) and focus an increased dose of radiation on just the breast tissue around the excision cavity (partial breast). Current accelerated partial breast irradiation (APBI) approaches include interstitial brachytherapy, intracavitary (balloon) brachytherapy, and accelerated external beam (three-dimensional conformal) radiotherapy. Intraoperative radiotherapy (IORT) is even shorter, with the entire treatment given as a single dose delivered immediately after surgery. Each approach has benefits and limitations. Planned randomized trials will shape how APBI is utilized in routine clinical practice. Some of the more important outcomes from these trials will be local toxicity, local and regional recurrence, and overall survival. If APBI is ultimately demonstrated to be as safe and effective as whole breast radiotherapy, breast conservation may become an even more appealing choice, and the overall impact of treatment may be further reduced for certain women with newly diagnosed breast cancer.

MEDICAL TREATMENT

Medical management of local disease depends on clinical and pathologic staging. Systemic therapy is indicated only for invasive (infiltrating) breast cancers.

In the past, systemic therapy was not offered to patients with stage I disease (tumors up to 2.0 cm). However, adjuvant chemotherapy and hormonal therapy have been shown to improve disease-free and overall survival in selected patients with node-negative disease.

The sequence of systemic therapy and definitive radiation therapy in women treated with breast-conserving surgery is a subject of continued clinical research. The use of concomitant chemotherapy and irradiation is not recommended due to the radiomimetic effects of chemotherapy and the potential for increased locoregional toxicity. Delaying chemotherapy up to 8-10 weeks after surgery does not appear to have a negative impact on the development of metastasis or survival.

Treatment regimens

Multiagent therapy with cyclophosphamide (Cytoxan, Neosar), methotrexate, and fluorouracil (5-FU, CMF regimen); cyclophosphamide, methotrexate, 5-FU, and prednisone (CMFP); sequential methotrexate and 5-FU (MF); and Adriamycin (doxorubicin) and cyclophosphamide (AC) has been used in patients with node-negative disease (Table 2). Hormonal therapy with tamoxifen (20 mg PO qd for 5 years) has been shown to be of value in women ≥ 50 years of age with estrogen- and/or progesterone-receptor–positive tumors. (See chapter 10 for further discussion about tamoxifen and the ATAC trial [Arimidex and Tamoxifen Alone or in Combination] as well as for adjuvant chemotherapy regimens in node-positive breast cancer [Table 1].)

TABLE 2: Adjuvant chemotherapy regimens in node-negative breast cancer

Regimen	Dose and frequency
MF	
Methotrexate	100 mg/m^2 IV on days 1 and 8
5-FU	600 mg/m^2 IV on days 1 and 8 (1 h after methotrexate)
Folinic acid	10 mg/m^2 PO q6h × 6 doses (24 h after methotrexate)
Repeat every 4 weeks for 12 cycles.	
CMF (Bonadonna regimen)	
Cyclophosphamide	600 mg/m^2 IV on day 1
Methotrexate	40 mg/m^2 IV on day 1
5-FU	600 mg/m^2 IV on day 1
Repeat every 3 weeks for nine cycles.	
or	
Cyclophosphamide	100 mg/m^2 IV on days 1-14
Methotrexate	40 mg/m^2 IV on days 1 and 8
5-FU	600 mg/m^2 IV on days 1 and 8
Repeat every 28 days for six cycles.	
CMFP	
Cyclophosphamide	100 mg/m^2 PO on days 1-14
Methotrexate	40 mg/m^2 IV on days 1 and 8
5-FU	600 mg/m^2 IV on days 1 and 8
Prednisone	40 mg/m^2 PO on days 1 and 14
Repeat every 4 weeks for six cycles.	
FAC	
5-FU	500 mg/m^2 IV on days 1 and 4 or 8
Adriamycin (doxorubicin)	50 mg/m^2 IV by continuous 72-h infusion on days 1-3 (or 50 mg/m^2 on day 1)
Cyclophosphamide	500 mg/m^2 IV on day 1
Repeat at 21-day intervals if hematologic recovery occurs for six cycles.	
CAF	
Cyclophosphamide	600 mg/m^2 IV on day 1
Adriamycin (doxorubicin)	60 mg/m^2 IV on day 1
5-FU	600 mg/m^2 IV on day 1
Repeat every 21-28 days.	
FEC	
5-FU	500 mg/m^2 IV on day 1
Epirubicin	100 mg/m^2 IV on day 1
Cyclophosphamide	500 mg/m^2 IV on day 1
Repeat every 21 days.	
AC	
Adriamycin (doxorubicin)	60 mg/m^2 IV on day 1
Cyclophosphamide	600 mg/m^2 IV on day 1
Repeat every 21-28 days depending on hematologic recovery for four cycles.	

Taxanes (ie, paclitaxel and docetaxel [Taxotere]) are now routinely used in the adjuvant therapy for node-positive breast cancer. The role of taxanes in node-negative disease is still evolving.

Node-negative tumors < 1.0 cm The reduction in the odds of recurrence and death with adjuvant therapy is similar in estrogen-receptor–negative and [node]-negative patients. Therefore, patients who have the lowest risk of recurrence are least likely to benefit from systemic treatment when the attendant risks of treatment are considered. None of the reported trials in node-negative breast cancer included women with tumors < 1.0 cm, and because of the low risk of recurrence (≤ 10%) in this group, systemic adjuvant therapy is not used routinely. Recent results from the NSABP in this group of patients are provocative in suggesting a potential benefit from systemic therapy.

In this validation study, the likelihood of distant recurrence in tamoxifen-treated patients with node-negative, estrogen receptor-positive breast cancer was tested using a reverse transcriptase (RT)-PCR assay of 21 prospectively selected genes (16 cancer-related genes and 5 reference genes) in paraffin-embedded tumor tissue. The levels of expression of the 21 genes were used in a prospectively defined algorithm to calculate a recurrence score and to determine a risk group for each patient. The proportions of patients categorized as having a low, intermediate, or high risk by the RT-PCR assay were 51%, 22%, and 27%, respectively. The Kaplan-Meier estimates of the rates of distant recurrence at 10 years in the low-, intermediate-, and high-risk groups were 6.8%, 14.3%, and 30.5%, respectively. The rate in the low-risk group was significantly lower than that in the high-risk group ($P < .001$). In a multivariate Cox model, the recurrence score provided significant predictive power that was independent of age and tumor size ($P < .001$). The recurrence score was also predictive of overall survival ($P < .001$) and could be used as a continuous function to predict distant recurrence in individual patients.

Node-negative tumors ≥ 1.0 cm The selection of a specific treatment program and the characteristics that predict risk of recurrence and death in women with node-negative breast cancer require further delineation and clarification in clinical trials. At present, women with tumors ≥ 1.0 cm who have poor histologic or nuclear differentiation, negative estrogen receptors, high S-phase percentage, or high Ki-67 can be considered appropriate candidates for adjuvant systemic therapy.

An update of the NSABP B-20 trial indicated a significant advantage in the estrogen-receptor–positive, node-negative population when chemotherapy with CMF or sequential MF is added to tamoxifen in the adjuvant setting. Patients receiving CMF plus tamoxifen appeared to derive the greatest benefit. Benefits with respect to both disease-free and overall survival have been reported for patients given chemotherapy and tamoxifen.

Chemotherapy and ovarian function suppression are both effective adjuvant therapies for patients with early-stage breast cancer. The efficacy of their sequential combination was investigated by the International Breast Cancer Study Group (IBCSG) Trial VIII. This study randomized more than a thousand pre-

and perimenopausal women with lymph node-negative breast cancer to receive either goserelin (Zoladex) for 24 months (n = 346), six courses of "classic" CMF chemotherapy (n = 360), or six courses of classic CMF followed by 18 months of goserelin (CMF then goserelin; n = 357). The primary outcome was disease-free survival. In this study, patients with estrogen-receptor–negative tumors achieved better 5-year disease-free survival rates if they received CMF (84% and 88% for CMF and CMF then goserelin, respectively) than if they received goserelin alone (73%). However, for patients with estrogen-receptor–positive disease, chemotherapy alone and goserelin alone provided similar outcomes (81% 5-year disease-free survival rates for both treatment groups), whereas sequential therapy provided a statistically nonsignificant improvement compared with either modality alone.

Follow-up of long-term survivors

There is no consensus among oncologists as to the optimal follow-up routine for long-term breast cancer survivors. Based on NCCN guidelines from September 2004, patients with stage 0 breast cancer should undergo a medical history and physical examination every 6 months for 5 years and then annually thereafter; mammography should be performed every year. Patients with stage I breast cancer should undergo medical history and physical examination every 4 to 6 months for 5 years and then annually thereafter. In stage I patients, mammography should be performed every 6 months in the ipsilateral breast after radiation therapy following breast-conservation surgery and then annually thereafter, including the contralateral breast; if mastectomy was performed, mammography should be done annually in the contralateral breast. Women receiving tamoxifen should undergo pelvic examination every 12 months if the uterus is present. All other follow-up evaluations are dictated by the development of symptoms.

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